Exhibit 143

Guidance for Industry

Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

DRAFT GUIDANCE

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For questions regarding this draft document contact David Jacobson-Kram at 301-796-0175.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Pharmacology and Toxicology

Guidance for Industry

Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

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U.S. Department of Health and Human Services
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Guidance for Industry[1]
Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to inform pharmaceutical manufacturers of the Food and Drug Administration's (FDA's) current thinking regarding genotoxic and carcinogenic impurities in drug substances and drug products, including biologic products that are regulated by the Center for Drug Evaluation and Research (CDER). This guidance provides recommendations on how to evaluate the safety of these impurities during clinical development (investigational new drug applications (INDs)) and for marketing applications (new drug applications (NDAs), biologics license applications (BLAs), and abbreviated new drug applications (ANDAs)). This guidance provides recommended exposure thresholds on the clinical exposure to genotoxic or carcinogenic impurities. Also provided are additional testing and exposure threshold recommendations for situations where there are known or theoretical safety concerns based on available data, structural alerts, and/or assessment of the synthetic pathway.

This guidance is intended as an adjunct to the ICH guidances for industry *Q3A(R2) Impurities in New Drug Substances*, *Q3B(R2) Impurities in New Drug Products*, and *Q3C(R3) Impurities: Residual Solvents* that deal with the topic of impurities in a more general fashion.[2] This guidance provides specific recommendations regarding the safety qualification of impurities with known or suspected genotoxic or carcinogenic potential while the ICH guidances provide only general direction. This guidance addresses synthetic impurities and degradants in drug substances, but does not otherwise address the genotoxicity or carcinogenicity of actual drug substances or intended drug product ingredients. This guidance also applies to known starting materials or anticipated reaction products.

[1] This guidance has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See http://www.fda.gov/cder/guidance/index.htm. The FDA has incorporated revision 3 (R3) of ICH Q3C into the guidance for industry *Q3C — Tables and List*, which is posted on the CDER guidance Web site.

This guidance describes a variety of ways to characterize and reduce the potential lifetime cancer risk associated with patient exposure to genotoxic and carcinogenic impurities both during clinical development and after approval. These approaches include:

- Changing the synthetic and/or purification routes to minimize the formation and/or maximize the removal of the relevant impurity.

- Allowing a maximum daily exposure target of 1.5 µg per day for the relevant impurity as a general target for marketed products, though higher levels may be acceptable during clinical development. Certain impurities with structural alerts suggesting particularly high genotoxic and carcinogenic potential would not be appropriate for this general threshold approach and would need to be evaluated on a case-by-case basis.

- Further characterizing the genotoxic and carcinogenic risk via mechanism of action or weight-of-evidence approaches, or through additional studies to better support appropriate impurity specifications.

This guidance also applies to drug products approved before the issuance of this guidance, but only in the presence of a specific safety signal that suggests the potential for an increased carcinogenic risk associated with the presence of an impurity or degradant, or with regard to a supplemental application for a previously approved drug product that proposes a significant change in the drug product's approved labeling that suggests the potential for an increased carcinogenic risk associated with the presence of an impurity or degradant (e.g., new indication, new dosage regimen, longer duration of use). Applicants also should take these recommendations into consideration when preparing supplemental manufacturing submissions to NDAs, BLAs, and ANDAs, such as submissions proposing new formulations or new synthetic routes. Although this guidance applies to impurities present in biologic products regulated by CDER, it is noted that, in most cases, the genotoxicity assays conducted for small molecule pharmaceuticals are not applicable to biopharmaceuticals. Likewise, the standard assessment of the genotoxic potential of impurities in biopharmaceuticals may not be appropriate in many cases since they may include residual host cell proteins and nucleic material, fermentation components, and bacterial and viral components and do not include organic chemicals typically found in small molecule manufacturing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Compounds that have been demonstrated to induce genetic mutations, chromosomal breaks, and/or chromosomal rearrangements are considered genotoxic and have the potential to cause

cancer in humans. Exposures to even low levels of these impurities may be of significant concern. Therefore, the identification limits provided in ICH Q3A(R2) and ICH Q3B(R2) may not be acceptable for genotoxic or carcinogenic impurities. For instance, under some scenarios the limits in these ICH guidances would allow a genotoxic or carcinogenic impurity to be present in a drug product at a level resulting in exposures up to 3,000 µg per day without needing identification. Although genotoxic and carcinogenic properties can be acceptable for some active pharmaceutical ingredients (APIs) depending on clinical circumstances (e.g., cancer chemotherapies), impurities in drug substances and drug products generally do not have beneficial effects and may impose a risk without associated benefit. Therefore, manufacturers should strive to achieve the lowest levels of genotoxic or carcinogenic impurities that are technically feasible and/or levels that convey no significant cancer risk.

Currently available guidances that address issues related to impurities and residual solvents include ICH Q3A(R2), ICH Q3B(R2), and ICH Q3C(R3). In addition, the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) published a guideline regarding limits of genotoxic impurities.[3] These documents are discussed below to provide a background to this guidance, but the inclusion of the EMEA guideline in this background discussion should not be interpreted as an FDA endorsement of that document.

A. ICH Guidances for Industry Relating to Drug Impurities and Residual Solvents

ICH Q3A(R2) and ICH Q3B(R2) address the issue of impurities in drug substances and drug products, respectively. ICH Q3A(R2) addresses the identification and qualification of impurities in drug substances approved after the issuance of the guidance, and ICH Q3B(R2) addresses only those impurities in drug products approved after the issuance of the guidance that are classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system. These guidances define an impurity as any component of the drug substance or drug product other than the chemical entity that makes up the drug substance or an excipient in the drug product. Depending on the quantity of drug substance or drug product to which a patient is exposed, these guidances recommend thresholds for the identification, reporting, and qualification of impurities. *Qualification*, as defined by the two guidances, is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity (or degradation product) or a given impurity (or degradation) profile at the level(s) specified.[4] Higher or lower thresholds for qualification can be considered appropriate based on scientific rationale and level of concern.[5]

These guidances recommend when, after consideration of factors such as the patient population and duration of use, qualification studies of an impurity are appropriate. Part of the battery of tests used to qualify an impurity could include assays to determine whether the impurity is

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[3] Guideline on the Limits of Genotoxic Impurities (EMEA guideline), June 2006 (http://www.emea.europa.eu).

[4] See the Glossary sections in ICH Q3A(R2) and ICH Q3B(R2).

[5] See ICH Q3A(R2), section VII, and ICH Q3B(R2), section VI.

genotoxic.[6] These guidances also recommend that, when considered appropriate, assays to assess genotoxic potential include the "minimum screen" of in vitro assays: a gene mutation assay and a chromosomal aberration assay.[7] ICH Q3A(R2) indicates that "such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate."[8] A similar recommendation is included in ICH Q3B(R2).

It should be noted, however, that allowing genotoxicity assessment of the impurity as it is present with the drug substance, rather than in isolation, renders the genotoxicity assessments much less sensitive. For example, the potent mutagens that are typically used as positive controls in the bacterial mutation assay, such as 9-aminoanthracene and methyl methanesulfonate, when present with a noncytotoxic drug substance at the minimal level for qualification, would not be detected by these genotoxicity assays because the maximum concentration of the impurity at the limit concentration of the drug substance would not be sufficient to produce a genotoxic response in the assays. If the drug substance is cytotoxic, this approach of assessing the impurity as it is present with the drug substance would be even more insensitive, since the drug's toxicity would further limit the level at which the impurity could be tested.

Although the ICH guidances provide some recommendations on the types of tests that should be conducted, the guidances do not provide specific recommendations on how to proceed if one or both of the genetic toxicology tests are positive; they simply state that additional testing, removal of the impurity, or lowering the level of the impurity should be considered.

ICH Q3C(R3) recommends acceptable concentration limits or permissible daily exposures for various classes of solvents, which are one type of impurity. The guidance does not, however, include a recommendation on limiting exposure based upon concerns for genotoxic potential. The guidance recommends only that mathematical models be used for setting exposure limits in cases where reliable carcinogenicity data are available.

The ICH guidances on impurities and residual solvents do not apply to drug substances or drug products used during the clinical research stages of development.

B. EMEA Proposed Guideline on Limits of Genotoxic Impurities

In June 2006, the EMEA's CHMP published a guideline on the limits of genotoxic impurities in support of a marketing application.[9] A subsequent CHMP safety working party published a

[6] See ICH Q3A(R2), section VII and Attachment 3, and ICH Q3B(R2), section VI and Attachment 3.

[7] Ibid.

[8] See ICH Q3A(R2), section VII.

[9] EMEA guideline (http://www.emea.europa.eu)

question and answers document to provide clarification on the 2006 guideline.[10] This guideline recommends dichotomizing genotoxic impurities into those for which there is "sufficient (experimental) evidence for a threshold-related mechanism" and those "without sufficient (experimental) evidence for a threshold-related mechanism." The genotoxic impurities with sufficient evidence for a threshold-related mechanism would be addressed using methods outlined in ICH Q3C(R3) for Class 2 solvents. This approach calculates a "permitted daily exposure," which is derived using the "no observed effect level" or, alternatively, the "lowest observed effect level" from the most relevant animal study and incorporating a variety of uncertainty factors. Examples of genotoxic compounds that might fall into this category include compounds that induce aneuploidy by interfering with the mitotic spindle, compounds that interfere with the activity of topoisomerase, and/or compounds that inhibit DNA synthesis.

For genotoxic impurities without sufficient evidence for a threshold-related mechanism, the guideline proposes a policy of controlling levels to "as low as reasonably practicable" (called the *ALARP principle*). The ALARP approach specifies that every effort should be made to prevent the formation of such impurities during drug substance synthesis and, if that is not possible, technical effort should be made post-synthesis to reduce impurities (e.g., purification steps). Compounds that fall into this category are those that interact with DNA either directly or indirectly, such as alkylating agents, intercalating agents, or agents that can generate free radicals. Since any exposure to these agents can convey some level of carcinogenic risk, and since complete elimination of genotoxic impurities from drug substances is often unachievable, the presence of a concerning impurity requires the implementation of a concept of an acceptable risk level. Methods for the derivation of acceptable risk levels are discussed in ICH Q3C(R3), Appendix 3, in reference to Class 1 carcinogenic solvents.

Although the approach described above is acceptable, in most instances mechanistic data sufficient to allow for an assessment of whether there is a threshold mechanism are lacking. Furthermore, it is relatively uncommon for there to be sufficient data to allow for a quantitative risk assessment. The EMEA guideline recognizes these limitations and, therefore, proposes the use of a "threshold of toxicological concern" (TTC) for genotoxic impurities. The TTC refers to a threshold exposure level to compounds that does not pose a significant risk for carcinogenicity or other toxic effects. The EMEA guideline recommends a TTC of 1.5 µg per day for all but a highly potent subset of compounds. This threshold corresponds to an incremental 10^{-5} lifetime risk of cancer, a risk level that the EMEA considers justified because of the benefits derived from pharmaceuticals. The guideline indicates that a TTC value higher than 1.5 µg per day may be acceptable based on a weight-of-evidence approach to the profile of genotoxicity results, in situations where the anticipated human exposure will be short-term, for the treatment of life-threatening conditions, when life expectancy is less than 5 years, or where the impurity is a known substance and human exposure will be much greater from other sources. The derivation of the TTC is discussed in more detail in section IV.B.1.

The approach taken in the EMEA guideline for setting an exposure limit for genotoxic or carcinogenic impurities in drug products in support of a marketing application is reasonable. However, issues regarding the presence of genotoxic or carcinogenic impurities often occur

[10] Question & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities, June 2008 (http://www.emea.europa.eu)

during the clinical development stages. Therefore, this guidance provides recommendations for acceptable exposure thresholds during clinical development as well as for marketing applications.

III. RECOMMENDED APPROACHES FOR INITIAL ASSESSMENT OF GENOTOXIC POTENTIAL OF IMPURITIES

If adequate data characterizing genotoxic and carcinogenic potential are not already available, impurities identified in drug substances or drug products at levels exceeding the stated qualification thresholds in the relevant ICH guidances should be assessed for genotoxic potential in an initial minimal screen. Assays conducted with the impurity in isolation are recommended. However, studies with the drug substance containing, or spiked with, the impurity can be considered in cases where it can be demonstrated that synthesizing sufficient amounts of the impurity is infeasible.

As mentioned, the ICH guidances on impurities do not apply to drug substances or drug products for use in clinical trials. However, in cases where the presence of an impurity with genotoxic or carcinogenic potential is identified or where such an impurity may be expected based on the synthetic pathway, steps should be taken during the clinical development stage to address safety concerns associated with these impurities.

If an impurity that is present at levels below the ICH qualification thresholds is identified, the impurity should be evaluated for genotoxicity and carcinogenicity based on structural activity relationship (SAR) assessments (i.e., whether there is a *structural alert*). This evaluation can be conducted via a review of the available literature or through a computational toxicology assessment; commonly used software includes MDL-QSAR, MC4PC, and Derek for Windows. The conduct of an in vitro mutation assay (i.e., bacterial reverse mutation assay) generally would be an acceptable initial screen for impurities with an identified alert, since positive signals in computational toxicology programs are often derived from the results of bacterial mutation assays and mutagenic carcinogens are considered to operate through nonthreshold-related mechanisms. An assessment in a mammalian cell assay may be needed for impurities with specific structural groups, such as carbamates, that are not well characterized in bacterial assays, or for compounds that are toxic to *E. coli* and *Salmonella*, such as antibiotics.

If the initial evaluation of the genotoxic potential of an impurity is negative, no further genotoxicity studies are recommended and the impurity should be considered to be adequately qualified regarding its genotoxic potential. It should be noted that in cases where it is necessary from a feasibility standpoint to conduct the assays with the drug substance containing, or spiked with, the impurity, the proposed acceptance criterion should be commensurate with the level of impurity observed in clinical, stability, and/or production batches, taking into consideration the manufacturing and analytical variability. This acceptance criterion should not exceed the level present in the drug batch used in the genotoxicity assay and should be supported by the relevant qualification thresholds discussed in the ICH guidances or supporting general toxicity information.

In some cases, the structure of an impurity leading to the structural alert is shared with the API. The genotoxic potential of such an impurity can be evaluated through the standard testing of the API if the chemical environment for the alerting structure of the compounds is deemed comparable for the reactivity potential.

IV. RECOMMENDED APPROACHES FOR HANDLING GENOTOXIC AND CARCINOGENIC IMPURITIES

Positive results in one or more genotoxicity assays or other information indicating a carcinogenic potential, such as positive data from a carcinogenicity study with the impurity, should be addressed further. Recommended approaches for handling genotoxic or carcinogenic impurities are described in this section and are summarized in Table 2 at the end of section IV.C. A decision tree is also included in Appendix A.

A. Prevention of Genotoxic and Carcinogenic Impurity Formation

Since drug-related impurities presumably provide limited, if any, therapeutic benefits and because of their potential to cause cancer in humans, every feasible technical effort should be made to prevent the formation of genotoxic or carcinogenic compounds during drug substance synthesis or drug product manufacturing. However, we recognize that completely preventing the formation of or removing an impurity of concern may not be possible in many cases.

B. Reduction of Genotoxic and Carcinogenic Impurity Levels

In lieu of completely preventing the formation of a genotoxic or carcinogenic impurity, steps to reduce the level of impurity present in the drug substance or drug product should be considered. The following sections discuss acceptable thresholds to support safety during clinical development and for a marketing application. Analytical methodologies should be used that can adequately identify impurities of concern at levels associated with the relevant qualification thresholds. This threshold approach should be applied only in the absence of adequate qualification data (data that establish the biological safety of an impurity at the level specified) for the given impurity.

1. Acceptable Levels to Support Marketing Applications

In general, an exposure level of 1.5 µg per person per day for each impurity can be considered an acceptable qualification threshold for supporting a marketing application. Any impurity found at a level below this threshold generally should not need further safety qualification for genotoxicity and carcinogenicity concerns. The threshold is an estimate of daily exposure expected to result in an upper bound lifetime risk of cancer of less than 10^{-6} (one in a million), a risk level that is thought to pose negligible safety concerns. The threshold was based on an analysis of the carcinogenic potencies of 477 chemicals and was derived from the probability distribution of carcinogenic potencies of those compounds.[11] Subsequent analyses of an

[11] Fiori, JM and RD Meyerhoff, 2002, Extending the Threshold of Regulation Concept: De Minimis Limits for Carcinogens and Mutagens, Reg Toxicol Pharmacol, 35, 209-216.

expanded carcinogenic potency database of more than 700 carcinogens further confirmed the threshold.[12] An additional analysis of subsets of highly potent carcinogens suggested that a threshold of 0.15 µg per day, corresponding to a 10^{-6} lifetime risk of cancer, may be more appropriate for chemicals with structural alerts for potential genotoxicity.[13] However, there are some compounds containing certain structural groups (aflatoxin-like-, N-nitroso-, and azoxy-structures) that have extremely high carcinogenic potency and are excluded from the threshold approach.

Federal regulatory agencies in the United States, such as the Environmental Protection Agency (EPA) (in the context of ambient water quality criteria), typically use a 10^{-6} lifetime risk of cancer to determine *negligible* risk from chemical exposures.[14] This approach supports an acceptable threshold level for genotoxic or carcinogenic impurities of 0.15 µg per day. However, other regulatory bodies have proposed a 10^{-5} level as an acceptable cancer risk.[15,16] Given that there is an overriding expected benefit of an approved drug product, a daily exposure level of 1.5 µg per day, associated with a 10^{-5} lifetime risk of cancer, can be acceptable for most genotoxic or carcinogenic impurities for a marketing application. This level of exposure is expected to produce a negligible increase in carcinogenic risk based on the existing background rate of human cancer and the conservative nature of cancer risk assessments. Additionally, this threshold is considered to be low enough to ensure that the presence of a compound with an uncharacterized genotoxic or carcinogenic potential would not significantly alter the risk-benefit ratio of a drug product, even if the impurity is later shown to be a carcinogen.

The database from which the exposure threshold for genotoxic or carcinogenic impurities is derived includes studies that primarily use oral administration, though a smaller number use the inhalation route. Although the recommended threshold approach applies to all drug products regardless of the intended route of administration, the qualification threshold of 1.5 µg per day may not be appropriate for some routes (e.g., dermal, ophthalmic) because of the lack of a relevant database from which an exposure threshold can be derived. Applicants should contact specific drug review divisions regarding acceptable approaches in these cases.

As part of this threshold approach, applicants can conduct and provide to the FDA an SAR assessment to identify structural similarities to known carcinogens. In cases where significant structural similarities to a known carcinogen are identified, an estimate of the potential human

[12] Ibid.

[13] Kroes, R, AG Renwick, M Cheeseman, J Kleiner, I Mangelsdorf, A Piersma, B Schilter, J Schlatter, F Schothorst, JG Vos, and G Würtzen, 2004, Structure-Based Threshold of Toxicological Concern (TTC): Guidance for Application to Substances Present at Low Levels in the Diet, Food Chem Toxicol, 42, 65-83.

[14] U.S. Environmental Protection Agency, Office of Water and Office of Science and Technology, 2000, Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, document number EPA-822-B-00-004, section 1.5.3 (http://www.epa.gov/waterscience/humanhealth/method/complete.pdf).

[15] See EMEA guideline, section 5.2.3.

[16] World Health Organization Guidelines for Drinking-Water Quality, 2nd ed., Vol. 2, 1996, Health Criteria and Other Supporting Information, Geneva, World Health Organization, section 12.4.2 (http://www.who.int/water_sanitation_health/dwq/gdwq2v1/en/index1.html).

cancer risk can be calculated based on the available information for the confirmed carcinogen. This assessment can result in an increase in the acceptable exposure threshold for impurities that are highly similar to carcinogens with relatively low potency, or a reduction in the limit for impurities that are highly similar to relatively potent carcinogens.

The EPA guidance *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (EPA/630/R-03/003F) regarding cancer susceptibility in pediatric populations indicates that children exposed to mutagenic carcinogens between age 0 (birth) and 16 have an increased cancer risk over a 70-year lifetime when compared to adults.[17] EPA concludes that cancer risks generally are higher from early-life exposure than from similar exposure durations later in life and recommends the application of adjustment factors to risk calculations to account for this observation. EPA recommends an adjustment factor of 10 for exposures before 2 years of age (i.e., spanning a 2-year time interval from the first day after birth up until a child's second birthday), which represents an approximation of the weighted geometric mean tumor incidence ratio from juvenile or adult exposures in repeated dosing studies. In the absence of data to calculate a specific dose-response adjustment factor for exposures between 2 and less than 16 years of age, EPA recommends an adjustment factor of 3, which represents an intermediate level of adjustment and reflects a midpoint between the 10-fold adjustment for the first two years of life and no adjustment (i.e., 1-fold) for adult exposures. However, the EPA guidance acknowledges that the resultant increases in cancer risk are relatively small for exposures that continue with fair uniformity over a lifetime. We recommend that this increase in susceptibility to carcinogens in pediatric populations be considered when determining the acceptable impurity level for a given drug product.

The threshold approach for genotoxic or carcinogenic impurities limits the likelihood that any individual impurity in a given drug product will present more than a 10^{-5} excess cancer risk, but the approach is not intended to ensure an aggregate excess cancer risk of less than 10^{-5}. This means the threshold approach to individual impurities is not intended to limit the overall excess cancer risk to 10^{-5} from all impurities in a single drug product or from multiple drug products concomitantly administered. As discussed above, this approach is consistent with approaches taken by various regulatory bodies such as EPA, World Health Organization, and EMEA in implementing threshold levels for carcinogenic risk when no benefit from the expected exposure is perceived. However, in cases where a class or family of structurally similar impurities is identified and is expected to have similar mechanisms resulting in their genotoxic or carcinogenic potential, the total daily exposure to the related compounds should be evaluated relative to the recommended threshold exposure.

We recognize that drug products are often indicated for short-term use. However, for most drugs, these threshold considerations still apply since a drug may be used multiple times by the same individual or may be used outside of its approved indication. A detailed rationale should be provided to the FDA to support limits higher than generally considered appropriate for a marketing application.

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[17] See http://cfpub.epa.gov/ncea/index.cfm.

2. *Acceptable Levels during Clinical Development*

The previous section describes the qualification threshold for genotoxic or carcinogenic impurities in support of a marketing application. Issues related to genotoxic impurities also can arise during a drug product's clinical development period and can affect the assessment of safety for conducting the program. Some flexibility in the previously described threshold level can be applied during the investigational stages, since clinical trials vary widely in duration from short-term (single dose to 4 weeks) to years and the qualification threshold for a marketing application is based on lifetime risk estimates. On the other hand, it should be recognized that during early clinical development, a benefit of the drug cannot be assumed. We recognize that the ability to identify and control drug-related impurities during early developmental stages is limited because of issues related to scale and maturity of production processes. Taking all these considerations into account, higher daily levels of exposure to potentially genotoxic impurities may be acceptable during the clinical development of the drug product compared to what is appropriate for a marketed drug product.

Bos et al. reviewed the derived cancer risk from short-term, high-dose exposure to a genotoxic carcinogen relative to the same cumulative dose distributed over a lifetime (virtually safe dose).[18] Briefly, the authors state that only a limited number of animal studies have assessed the comparative tumor incidence from short-term versus long-term exposures with similar cumulative doses. From those studies that do exist, dose rate correction factors (factors by which a specific dose of a chemical carcinogen at long-term, low-dose rates should be multiplied to derive the expected tumor incidence from short-term, high-dose rates) ranged from unity to 8.3. The authors conclude that the most pragmatic approach to calculate acceptable short-term exposures to known genotoxic carcinogens is to linearly extrapolate the short-term exposure from the acceptable lifetime exposure or virtually safe dose.

Acceptable daily intakes of genotoxic impurities during clinical development are presented in Table 1, based on the linear extrapolation approach described by Bos et al. The impurity threshold exposures for exposure durations of up to 12 months are based on a 10^{-6} cancer risk level (0.15 µg per day for a lifetime exposure), since these trials often include healthy subjects for whom there is no expected health benefit and the efficacy of the drug may still be uncertain. The values are derived from a linear extrapolation from the qualification threshold using the maximum duration of dosing for each time period specified in Table 1. In addition, these values incorporate an uncertainty factor of 2 to allow for deviations from the linear extrapolation model. For trials greater than 1-year duration, the threshold value is identical to the threshold for a marketing application and is based on a 10^{-5} cancer risk level (1.5 µg per day derived from lifetime exposures); subjects in these trials generally have the condition or disease being studied and are more certain to derive benefit from the treatment than subjects in early trials. When determining the acceptable impurity threshold exposure, the specifics of the patient population in the clinical trial should be evaluated.

[18] Bos, PMJ, B Baars, TM Marcel, and MTM van Raaij, 2004, Risk Assessment of Peak Exposure to Genotoxic Carcinogens: A Pragmatic Approach, Toxicol Letters, 151:43-50.

Table 1: Acceptable Qualification Thresholds for Genotoxic and Carcinogenic Impurities

	Duration of Clinical Trial Exposure					
	< 14 days	**14 days to 1 mo**	**1 mo to 3 mos**	**3 mos to 6 mos**	**6 mos to 12 mos**	**> 12 mos**
Genotoxic and carcinogenic impurity threshold (µg/day)	120	60	20	10	5	1.5

C. Additional Characterization of Genotoxic and Carcinogenic Risk

In cases where attempts to prevent the formation of an impurity of concern and/or to reduce the amount of the impurity to an acceptable level as per Table 1 are not possible, further characterization of the genotoxic and carcinogenic potential should be conducted. The guidance for industry and review staff *Recommended Approaches to Integration of Genetic Toxicology Study Results* describes the FDA's current thinking regarding appropriate additional evaluations that can be conducted.[19] Briefly, these concepts include the consideration of the mechanism of action, weight of evidence, or the conduct of additional supportive studies. These concepts also can be considered relevant for genotoxic impurities.

In addition to the above considerations, the conduct of an SAR evaluation of an impurity may provide useful information. When a significant structural similarity to a known carcinogen is identified, the drug substance and drug product acceptance criteria (typically in units of parts per million or percent) can be set at a level that is commensurate with the risk assessment specific to that of the known compound. As noted previously, the proposed factors should be considered in light of manufacturing batch data.

Table 2 summarizes the recommended approaches for characterizing the presence and addressing the safety of genotoxic and carcinogenic impurities depending on the clinical development stage.

[19] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at http://www.fda.gov/cder/guidance/index.htm.

Table 2: Recommended Approaches Based on Development Stage

Clinical Development Stage	Recommended Approach
IND	• Evaluate identified impurities for genotoxic and carcinogenic risk via SAR assessment • Conduct assay for the presence of anticipated genotoxic and carcinogenic impurities • If impurity with genotoxic and carcinogenic potential is identified: – Modify synthetic pathway to eliminate the impurity, if possible OR – Conduct genotoxicity assays to characterize the genotoxic potential if not already known AND/OR – Set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or relevant qualification threshold (see Table 1)
Marketing application (NDA, BLA, or ANDA)	• Evaluate identified impurities for genotoxic and carcinogenic risk via SAR assessment • If impurity with genotoxic and carcinogenic potential is identified: – Conduct genotoxicity assays to characterize the genotoxic potential if not already known AND/OR – Set specification to that associated with a potential daily impurity exposure supported by compound-specific risk assessment or 1.5 µg per day threshold

D. Considerations for Flexibility in Approach

The previous sections are intended to be general recommendations to consider when developing a drug product in which a potentially genotoxic or carcinogenic impurity is identified. We recognize that these approaches may not necessarily apply to every development program, and flexibility in the application of these recommendations may be appropriate. When applying the recommendations, consideration should be given to the drug product's clinical development stage, the maximum duration of drug administration at that stage, the proposed indication (e.g., treatment of a life-threatening condition versus a less serious condition), the patient population (e.g., adults versus children), and the structural similarity of an impurity to a compound of known carcinogenic potency. In some of these cases, acceptance criteria higher than the recommended thresholds can be supported in the presence of a potential pharmacological benefit to patients. In rare cases, such as in the presence of highly potent carcinogens, decreases in the threshold also may be warranted. The appropriateness of a flexible approach should be informed by the feasibility of controlling impurity levels and the capabilities of the current process.

458 **APPENDIX A: DECISION TREE FLOW DIAGRAM**

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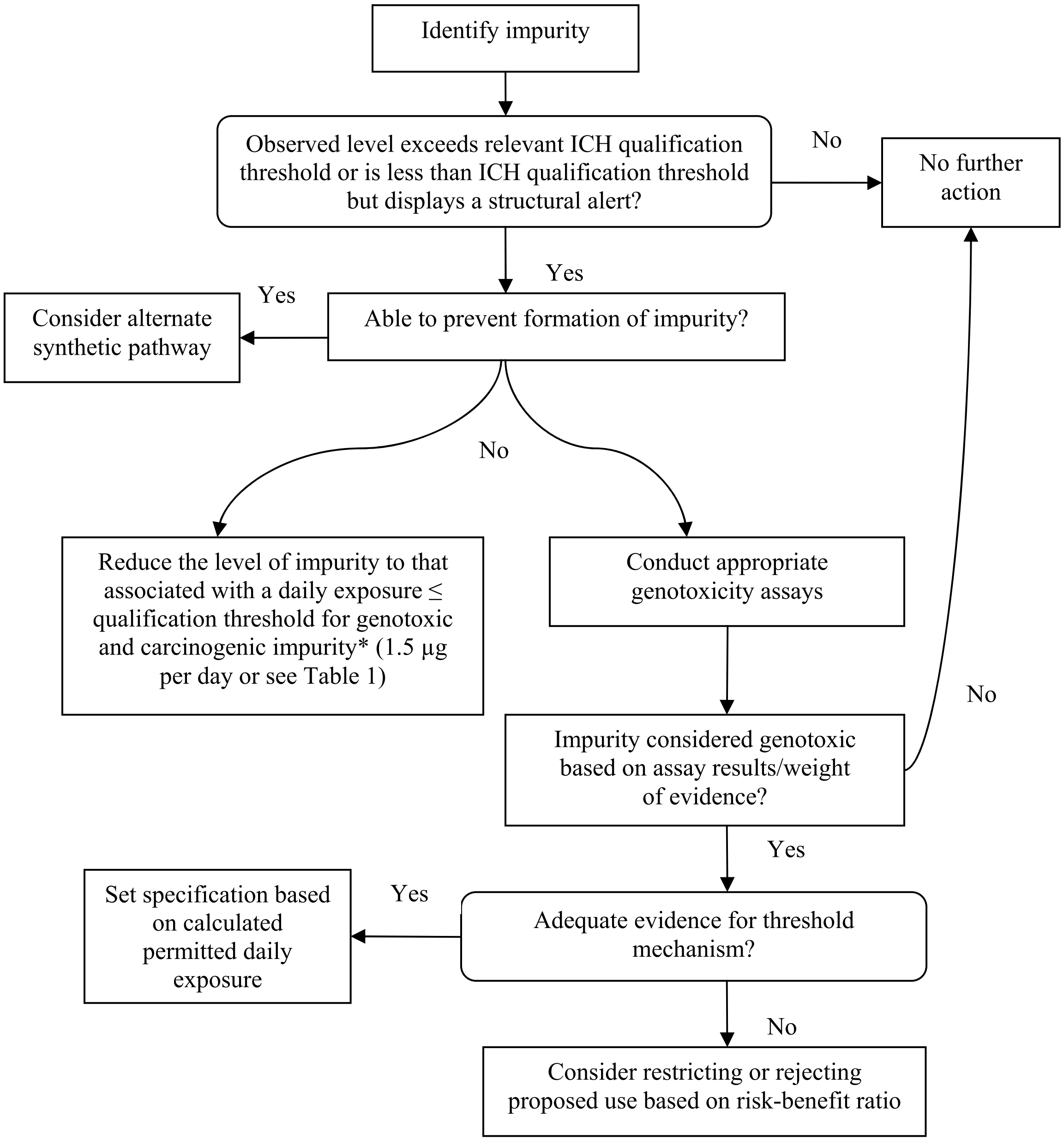

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*Safety threshold approach for genotoxic and carcinogenic impurities is not applicable to compounds with adequate data to derive compound-specific risk assessment or for those with SARs to high potency carcinogens. In addition, the approach may not be appropriate for some routes of administration (e.g., dermal, ophthalmic) because of the lack of a relevant database from which a threshold limit can be derived.